CA724 predicts overall survival in locally advanced gastric cancer patients with neoadjuvant chemotherapy

Yilin Tong
Liaoning Cancer Institute and Hospital https://orcid.org/0000-0001-6395-6534
Yan Zhao
Liaoning Cancer Institute and Hospital
Zexing Shan
Liaoning Cancer Institute and Hospital
Jianjun Zhang (zhangjianjun@cancerhosp-ln-cmu.com)
https://orcid.org/0000-0001-6672-2469

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Abstract

Background: Serum tumor markers are of great importance in diagnosis, prognostic predicting and recurrence monitoring in gastrointestinal malignancy, including AFU, AFP, CEA, CA199, CA125 and CA724. However, their significances in gastric cancer (GC) patients with neoadjuvant therapy (NCT) are still uncertain. The aim of this study is to evaluate the predictive value of these six tumor markers in locally advanced GC patients with NCT and curative surgery. Methods: 290 locally advanced GC patients with NCT and D2 radical gastrectomy were retrospectively analyzed. Their tumor markers before (pre-) and after (post-) NCT and pathological characters were exacted from the database in our hospital. The optimal cutoff values of six tumor markers were calculated by ROC and Youden index. Their predictive significances were analyzed and survival curves on overall survival (OS) were obtained by Kaplan-Meier method. Associations between categorical variables were explored by Chi-square test or Fisher's exact method. Multivariate analyses were performed by Cox regression model. Results: Not only the pre- and post- CA199, CA125 and CA724 could predict the OS respectively, but also the changes (diff-) between post- and pre- groups were related to the prognosis ($P < 0.05$). In multivariable analysis, only pre- ($P = 0.016$) and post-CA724 ($P = 0.033$) remained significant, and the significance of diff-CA724 was on borderline ($P = 0.085$). Besides, pre- and post-CA199, CA125 and CA724 were associated with the metastasis of lymph node (N- vs N+) and pathological stage (□-□ vs □) ($P < 0.05$). Post-CA724 was related to the invasion of vascular or lymphatic vessels ($P = 0.019$), and pre-CA724 was nearly remarkable ($P = 0.082$). However, AFU, AFP and CEA showed no association with survival ($P > 0.05$). Conclusions: CA724 is an independent factor to prognosis, and could be used to predict the ypN and ypTNM stage in locally advanced GC patients undergone NCT and curative resection.

Background

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third leading cause of cancer death worldwide[1]. Excellent outcomes could be expected from surgery alone when gastric cancer is diagnosed at early stage. However, in locally advanced GC patients, operation could not always lead to a satisfactory consequence, even with postoperative therapy[2]. Neoadjuvant chemotherapy (NCT) improves R0 resection rate and prognosis when compared with surgery alone or surgery with postoperative therapy[3], but the outcomes are blurred due to the differences in many factors such as tumor differentiation and Lauren classification. More indicators to assess the survival are urgently needed.

Serum tumor markers play an important role in diagnosis, prognostic predicting and recurrence monitoring in gastrointestinal malignancy. As studies claimed, AFU was considered to relate to liver metastasis in colorectal cancer[4]; AFP was associated with prognosis in gastric cancer patients undergone surgery alone[5]; preoperative CEA could predict the prognosis of pN0 GC patients[6]; CA199 was an independent prognostic factor in esophagogastric junction (GEJ) patients who experienced surgery alone[7], CA125 level was related to the degree of peritoneal dissemination and the existence of malignant ascites in GC patients with peritoneal metastasis[8], and CA724 was correlated with pTNM

stage in gastric carcinoma patients[9]. However, for GC patients underwent NCT, the evidence of these markers is still insufficient.

In this article, we reappraised the prognostic significance of the six serum tumor markers before and after NCT as well as the change in locally advanced GC patients, and explored their inner-relationships and their relations with pathological factors.

Methods

Between June 2010 and July 2016, patients with locally advanced gastric adenocarcinoma (including esophagogastric junction carcinoma) who underwent preoperative chemotherapy with or without postoperative treatment were identified from the database of our hospital. The inclusion criteria were as follows: (1) Histopathological evidence of gastric adenocarcinoma; (2) Locally advanced tumor (8th AJCC clinically staging □~□); (3) Underwent NCT with or without postoperative treatment; (4) Curative gastrectomy surgery with D2 lymph node dissection were performed. The patients underwent preoperative radiotherapy, or suffering from other malignant tumor were excluded.

Clinical data, pre- and post-NCT serum tumor markers including AFU, AFP, CEA, CA199, CA125 and CA724 levels, as well as postoperative pathological information of all patients were extracted from our database. The diff- indicated the difference between post- and the pre- groups.

The optimal cutoff values of all serum tumor markers and other continuous variables were calculated by ROC curves and Youden index. The relationships between discrete variables were computed by Chi-square test or Fisher's exact method, and their intensities were evaluated by coefficient of contingency (C value). Survival curves for overall survival were obtained using the Kaplan-Meier method, and log-rank test was used to compare survival differences. Cox regression analysis was used to assess the prognostic risk of tumor markers and pathological variables with OS, and the factors with P value ≤ 0.05 or with great importance in clinical diagnosis were included in multivariable analysis. OS was calculated as the time from the initial treatment time to death by any cause or last follow-up. Data was proceeded by SPSS 25.0 software.

Results

Patient characteristics

From 3196 patients in total, 290 patients matched the inclusion criteria. Their clinicopathological features were shown in **Table 1**. There were 215 males (74.1%) and 75 females (25.9%), with age range 25-77 years (median 59 years). For the tumor location, a majority of tumors located in L area (65.2%), while 8 (2.8%) in gastroesophageal junction (GEJ), and 24 (8.3%) in diffuse group. Most patients underwent preoperative therapy of SOX (73.8%), and the median cycle of NCT was 2 (range from 2-4). The median interval from the end of neoadjuvant treatment to the time of surgery was 4 weeks (range from 1-9). 31

(10.7%) patients refused to receive postoperative treatment. Median follow-up time of all patients was 41 months (range 3–91months).

Pathologically, the average number of removed lymph nodes was 27, and 100 (34.5%) patients had no lymph node metastasis. Nearly half of the patients (49.3%) presented with intestinal type, and only one fourth (25.2%) were well differentiated. Patients with vascular or lymphatic invasion (VOLI) accounted for 24.8%, while nervous invasion (NI) 23.4%.

Prognostic impact of levels of serum tumor markers

Because of the nature of retrospective studies, not all patients had six serum tumor markers. The number of patients whose markers were available before and after NCT were shown in **Supplementary Table 1**. The levels of pre- serum tumor markers were measured within 4 weeks before the beginning of NCT and the post- ones were measured within 2 weeks before gastrectomy.

The univariate analysis outcomes of every marker were listed in **Table 2**, and their survival curves were shown in **Figure 1,2,3**. These results indicated that for CA199, CA125 and CA724, all positive groups possessed worse prognosis ($P < 0.05$). While for AFU, AFP and CEA, there was no prognostic significance ($P > 0.05$).

In multivariate analysis, pre-, post-, and diff-CEA, CA199, CA125 and CA724 were included respectively (**Table 3**). In pre- and post- groups, CA724 remained its prognostic significance, while other markers were not. In diff- group, the P value for CA724 was closed to significant ($P = 0.085$).

Association within serum tumor markers

Because the significances of tumor markers were lost in multivariate analysis except for CA724, we analyzed the inter-connection between these markers. Their coefficients of contingency were shown in **Table 4**. In pre- group, the positive rates of CA199 ($P = 0.005$) and CA125 ($P = 0.015$) were significantly higher when CEA was positive, and the positive rates of CA125 ($P = 0.001$) and CA724 ($P = 0.002$) were significantly higher when CA199 was positive. However, for post- indicators, only the relation between CEA and CA125 was still remarkable ($P = 0.014$). Although associations also existed in diff-group, its C values were lower than the former groups.

Relationship between serum tumor markers and pathological factors

The correlations between markers and pathological factors were analyzed (**Table 5**). The lymph node metastasis rates of the positive group were significantly higher in pre- and post-CA199, CA125 and

CA724. In the diff- category, only diff-CA125 showed similar outcomes.

The ratio of ypTNM stage □ was significantly higher in positive group of pre- and post- CA199, CA125 and CA724.

In terms of VOLI, the invasion rate was significantly higher in positive team of post- CA724 (P = 0.019). In pre- group, the difference was close to significant (P = 0.082), while in diff- one, the significance was lost. For other markers, no associations were found. In addition, there were no relations between markers and NI.

Discussion

Serum tumor markers are widely applied in the diagnosis, therapeutic effect assessment and disease recurrence monitoring[9]. A series of studies have explored the diagnostic and prognostic value of various serum tumor markers for gastric cancer[10]. However, most of these researches based on the patients undergone surgery with or without posttreatment, with only a few focusing on the patients with NCT in gastric cancer[11, 12].

From other researches, CA125 was associated with R0 resection rate[13], recurrence and peritoneal dissemination[14] and OS in the unresectable advanced or recurrent GC patients[15]; CA199 was related to pN[7, 16-18] and pTNM stage[17], and CA724 possessed the larger area under the receiver operating curve, which meant a higher diagnostic efficiency[19]. However, none of their patients underwent NCT.

In our study, not only the levels of CA199, CA125 and CA724 before and after NCT could predict the prognosis, but also the differences were related to the outcomes. Similar results had been put forward by many researches in GC patients without NCT[8, 13, 19, 20]. Nevertheless, we found that only CA724 was an independent prognostic marker in multivariable analysis. Notably, this independent significance decreased in the diff- group, which was a little different with some studies. Zou et al.[11] claimed that the change of CA724 could reflect the therapeutic effect of NCT. Another paper supported that a decrease in CA724 could lead to a better prognosis[12]. The distinction might due to we included more pathological factors in multivariable analysis. Despite of this, CA724 was still more specific and sensitive than other markers for GC patients undergone NCT.

Although CA724 owned a higher diagnostic value in GC, its sensitivity was only about 45.0%[19]. Moreover, in China, CA724 was claimed to associate with Helicobacter pylori infection[21] and even geographical environment factors, such as temperature[22]. These indicated that it was not enough to evaluate the condition of patients merely depend on CA724. To solve this problem, a lot of work had been done. For example, TKI, an enzyme involved in the regulation of the mammalian cell cycle, was another choice of marker in gastric cancer[19]. Or, the combination of CA724 with CA199, CA125 and CEA could also improve the capability of diagnosis[9, 12, 19, 23].

With regard to the pathological factors, we found that CA199, CA125 and CA724 before and after NCT were all predict indicators for lymph node metastasis and ypTNM stage. In the previous articles, in GC patients who experienced curative gastrectomy, preoperative CA199 could predict the lymph node metastasis[17, 18] and the pTNM stage[17]. CA724 was associated with nodal involvement[9] and worse stage in advanced gastric cancer patients[19]. As supplementary, we confirmed these in patients with preoperative therapy. In addition, we found CA125 as well as the change of CA125 was also related to ypN and ypTNM stage.

In our study, the VOLI rate was significantly higher in post-CA724 positive group, while in pre- group, the P value was closed to significant. However, Sun et al.[12] suggested that pre-CA724 was related to vascular invasion. This might suggest that CA724 could be used to assess the lymphatic or vascular invasion, but more researches are needed to distinguish the accuracy between pre- and post- groups.

It was unexpected that CEA was not related to prognosis in our study. Although a team from Japan supported a similar result[7], a large number of studies suggested the opposite one[10, 16, 18, 24]. Nevertheless, our CEA positive rate was related to the rising of CA199 and CA125, which had been raised before[7, 19]. Notably, these connections weakened after the NCT, which probably meant that the preoperative treatment could blur these relationships.

The limitations still exist in this study. Firstly, due to the nature of retrospective research, some patients did not have all values of markers, which hindered the exploration of the combination of markers. Secondly, the sample size was not large. The sample number of AFU and AFP in every group were so small that they were not included in the further analysis. This limitation might also contribute to the reason why some P values were more than 0.05 but smaller than 0.1. Thirdly, we used the optimal cutoff value derived from Youden index, which disturbed the comparation with other studies.

Despite of these limitations, our study still possesses some merits. Our sample size is relatively small, but we forced on specific group of patients. Although the optimal cutoff values have been agreed in patients without preoperational treatment, whether the borderline would change due to neoadjuvant therapy is still unknown. We not only illuminated the prognostic significance of these tumor markers, but confirmed their effects to predict lymph node metastasis and pathological stage. These results are useful for assessing the condition of patients and further clinical decision.

Conclusions

CA724 before and after the neoadjuvant chemotherapy were both independent prognostic factors in GC patients undergone NCT and curative surgery. Pre- and post- CA724 could also be used to predict the lymph node metastasis and pathological stage. However, only the change of CA724 was statistically significant in the univariate analysis of prognosis.

Abbreviations

AFU: alpha-l-fucosidase; AFP: alpha-fetoprotein; CEA: Carcinoembryonic antigen; CA199: carbohydrate antigen 19–9; CA125: cancer antigen 125; CA724: carbohydrate antigen 72–4; ypTNM: Post-neoadjuvant therapy stage; pTNM: Pathological stage; GC: Gastric cancer; NCT: neoadjuvant therapy; OS: overall survival; AJCC: American Joint Committee on Cancer; VOLI: vascular or lymphatic invasion; NI: nervous invasion.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Faculty of Science Ethics Committee at Liaoning Cancer Hospital and Institute (Cancer Hospital of China Medical University)

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are not publicly available due to the presence of identifiable patient information but are available from the corresponding author on reasonable request.

Competing interests

All authors declare that there is no conflict of interest.

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Authors' contributions

YT performed the majority of experiments and analyzed the data and drafted the manuscript; YZ reviewed and revised the manuscript; ZS assisted in collected and analyzed the data; JZ supervised the study and provided critical revision of the manuscript.

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Tables

Table 1 Clinicopathological characteristics

Characteristics	No. of patients	Percent
Gender		
Male	215	74.1
Female	75	25.9
Age		
65	221	76.2
≥65	69	23.8
Blood type		
A	101	34.8
B	73	25.2
AB	28	9.7
O	88	30.3
Smoking		
No	128	44.1
Yes	162	55.9
Drinking		
No	194	66.9
Yes	96	33.1
Family history		
No	230	79.3
Yes	60	20.7
Tumor Location		
GEJ	8	2.8
U	32	11.0
M	54	18.6
L	172	59.3
Diffuse	24	8.3
Tumor Size (cm)		
<5	115	39.7
≥5	175	60.3
ypT		
0	9	3.1
1-2	57	19.6
3-4	224	77.3
ypN		
0	100	34.5
1	49	16.9
2	79	27.2
3	62	21.4
ypTNM		
	53	18.3
	72	24.8
	165	56.9
Histological type		
Adenocarcinoma	186	64.1
Mucinous or Signet ring cell	104	35.9
Lauren Classification		
Intestinal	143	49.3
Diffuse or Mixed	147	50.7
Grade of differentiation		
Well	70	25.2
Moderate or Poor	220	74.8
Vascular or lymphatic invasion		
No	218	75.2
Yes	72	24.8
Nervous invasion		

No	222	76.6
Yes	68	23.4
Neoadjuvant therapy		
SOX	214	73.8
XELOX	21	7.2
FOLFOX	55	19.0
Adjuvant treatment		
No	31	10.7
Yes	259	89.3

Table 2 Univariate analysis of tumor markers

Tumor marker	Hazard ratio (95% CI)	P value
pre-AFU>45.1	1.607 (0.504, 5.126)	0.423
pre-AFP>2.6	1.294 (0.810, 2.066)	0.280
pre-CEA>1.6	1.193 (0.841, 1.893)	0.322
pre-CA199>24.9	1.729 (1.187, 2.519)	**0.004**
pre-CA125>16	2.337 (1.515, 3.606)	**0.000**
pre-CA724>4.6	2.033 (1.391, 2.972)	**0.000**
post-AFU>40.9	0.995 (0.517, 1.915)	0.988
post-AFP>4.6	1.697 (0.958, 3.005)	0.070
post-CEA>3.3	1.220 (0.813, 1.831)	0.337
post-CA199>62.6	2.447 (1.515, 3.954)	**0.000**
post-CA125>11.2	2.187 (1.352, 3.536)	**0.001**
post-CA724>5.9	2.246 (1.460, 3.455)	**0.000**
diff-AFU>9.7	1.429 (0.762, 2.681)	0.266
diff-AFP>1.39	2.275 (0.946, 5.470)	0.066
diff-CEA>0.035	1.033 (0.698, 1.527)	0.872
diff-CA199>0.075	1.631 (1.099, 2.418)	**0.015**
diff-CA125>0.79	1.726 (1.065, 2.797)	**0.027**
diff-CA724>0.365	1.663 (1.056, 2.616)	**0.028**

Note: Units: AFU(U/L); AFP(ng/ml); CEA(ng/ml); CA199(U/ml); CA125(U/ml); CA724(U/ml)

Table 3 Multivariate analysis of all characteristics

Variable	pre-HR (95% CI)	P	post-HR (95% CI)	P	diff-HR (95% CI)	P
Age	1.054 (0.569, 1.952)	0.866	0.569 (0.257, 1.263)	0.166	0.742 (0.331, 1.664)	0.469
Tumor Location		0.138		**0.017**		0.398
U	1		1		1	
GEJ	0.273 (0.043, 1.722)	0.167	0.442 (0.054, 3.644)	0.448	0.700 (0.055, 8.892)	0.784
M	0.495 (0.180, 1.364)	0.174	0.098 (0.018, 0.541)	**0.008**	0.299 (0.046, 1.938)	0.205
L	0.503 (0.207, 1.222)	0.129	0.242 (0.075, 0.777)	**0.017**	0.644 (0.186, 2.228)	0.487
Diffuse	1.121 (0.401, 3.134)	0.828	0.753 (0.220, 2.584)	0.652	1.337 (0.296, 6.040)	0.706
Tumor Size (cm)	1.600 (0.782, 3.277)	0.198	1.707 (0.629, 4.633)	0.294	1.603 (0.583, 4.407)	0.361
ypT		0.336		0.073		0.148
0	1		1		1	
1-2	0.192 (0.014, 2.611)	0.215	0.082 (0.004, 1.781)	0.111	0.124 (0.005, 3.331)	0.214
3-4	0.346 (0.020, 5.895)	0.463	0.458 (0.013, 16.705)	0.671	0.581 (0.011, 29.832)	0.787
ypN		**0.003**		**0.001**		**0.003**
0	1		1		1	
1	6.958 (1.921,25.207)	**0.003**	51.682 (7.574, 352.668)	**0.000**	29.669 (3.114, 174.584)	**0.001**
2	9.513 (2.269,39.880)	**0.002**	44.946 (6.157, 328.089)	**0.000**	23.315 (3.114, 174.584)	**0.002**
3	16.023 (3.646,70.417)	**0.000**	59.818 (7.159, 499.801)	**0.000**	45.795 (5.722, 366.507)	**0.000**
ypTNM		0.493		0.073		0.139
	1		1		1	
	1.725 (0.253,11.758)	0.578	1.264 (0.089, 17.940)	0.863	1.376 (0.062, 30.412)	0.840
	0.881 (0.097, 8.037)	0.911	0.187 (0.008, 4.598)	0.304	0.254 (0.008, 8.278)	0.441
Histological type	0.579 (0.307, 1.091)	0.091	1.248 (0.567, 2.749)	0.582	0.919 (0.390, 2.166)	0.847
Lauren Classification	1.769 (0.973, 3.216)	0.062	0.985 (0.451, 2.154)	0.970	1.320 (0.529, 3.290)	0.552
Grade of differentiation	2.738	**0.025**	3.985	**0.036**	5.115	**0.016**

	(1.137, 6.594)		(1.091, 14.552)		(1.349,19.394)	
VOLI	1.665	0.077	4.714	**0.000**	2.627	**0.029**
	(0.947, 2.929)		(2.130, 10.433)		(1.103, 6.254)	
NI	1.020	0.945	1.053	0.878	1.255	0.550
	(0.572, 1.821)		(0.543, 2.044)		(0.596, 2.642)	
Adjuvant therapy	3.434	**0.003**	6.111	**0.001**	6.986	**0.001**
	(1.505, 7.834)		(2.007, 18.607)		(2.327,20.971)	
CEA	1.316	0.354	0.985	0.969	1.245	0.583
	(0.736, 2.352)		(0.450, 2.153)		(0.570, 2.715)	
CA19-9	1.009	0.976	1.621	0.318	1.183	0.683
	(0.545, 1.871)		(0.627, 4.190)		(0.528, 2.648)	
CA12-5	1.520	0.167	1.572	0.180	1.747	0.148
	(0.840, 2.750)		(0.811, 3.046)		(0.820, 3.721)	
CA72-4	2.158	**0.016**	2.402	**0.033**	2.049	0.085
	(1.157, 4.026)		(1.072, 5.382)		(0.905, 4.636)	

Note: VOLI: Vascular or lymphatic invasion; NI: Nervous invasion

Table 4 Coefficient of contingency (C value)

Markers				C value	P value
pre-CEA		-	+		
pre-CA199	-	104	96	0.169	**0.005**
	+	22	46		
pre-CA125	-	71	62	0.177	**0.015**
	+	17	34		
pre-CA199		-	+		
pre-CA125	-	109	27	0.230	**0.001**
	+	29	22		
pre-CA724	-	115	25	0.205	**0.002**
	+	52	30		
post-CEA		-	+		
post-CA199	-	152	57	0.125	0.052
	+	16	13		
post-CA125	-	67	20	0.185	**0.014**
	+	50	34		
post-CA724	-	85	27	0.133	0.069
	+	45	26		
post-CA199		-	+		
post-CA125	-	82	5	0.130	0.089
	+	71	11		
diff-CEA		-	+		
diff-CA199	-	73	47	0.155	**0.019**
	+	46	56		
diff-CA125	-	56	31	0.141	0.085
	+	29	29		
diff-CA199		-	+		
diff-CA125	-	50	37	0.198	**0.015**
	+	21	36		
diff-CA724	-	67	33	0.217	**0.004**
	+	28	35		

Note: Only results with $P \leq 0.1$ were listed

Table 5 Relationship between serum tumor markers and pathological factors

		N stage		P value	ypTNM		P value	VOLI		P value
		N-	N+		□-□	□		+	-	
pre-CA199	-	80	125	**0.017**	94	111	**0.042**	156	49	0.400
	+	16	53		22	47		49	20	
pre-CA125	-	62	74	**0.000**	71	65	**0.000**	102	34	0.116
	+	7	45		12	40		33	19	
pre-CA724	-	50	91	**0.030**	65	76	**0.004**	110	31	0.082
	+	18	65		22	61		56	27	
post-CA199	-	82	132	**0.003**	100	114	**0.003**	159	55	0.559
	+	3	26		105	138		23	6	
post-CA125	-	45	43	**0.001**	51	37	**0.003**	65	23	0.854
	+	22	62		30	54		61	23	
post-CA724	-	46	68	**0.016**	55	59	**0.024**	91	23	**0.019**
	+	17	56		23	50		47	26	
diff-CA199	-	45	79	0.674	55	69	0.620	96	28	0.267
	+	36	71		44	63		76	31	
diff-CA125	-	39	49	**0.035**	46	42	0.074	65	23	0.425
	+	16	43		22	37		40	19	
diff-CA724	-	32	69	0.901	44	57	0.212	74	27	0.726
	+	20	45		22	43		46	19	

Note: VOLI: Vascular or lymphatic invasion

Figures

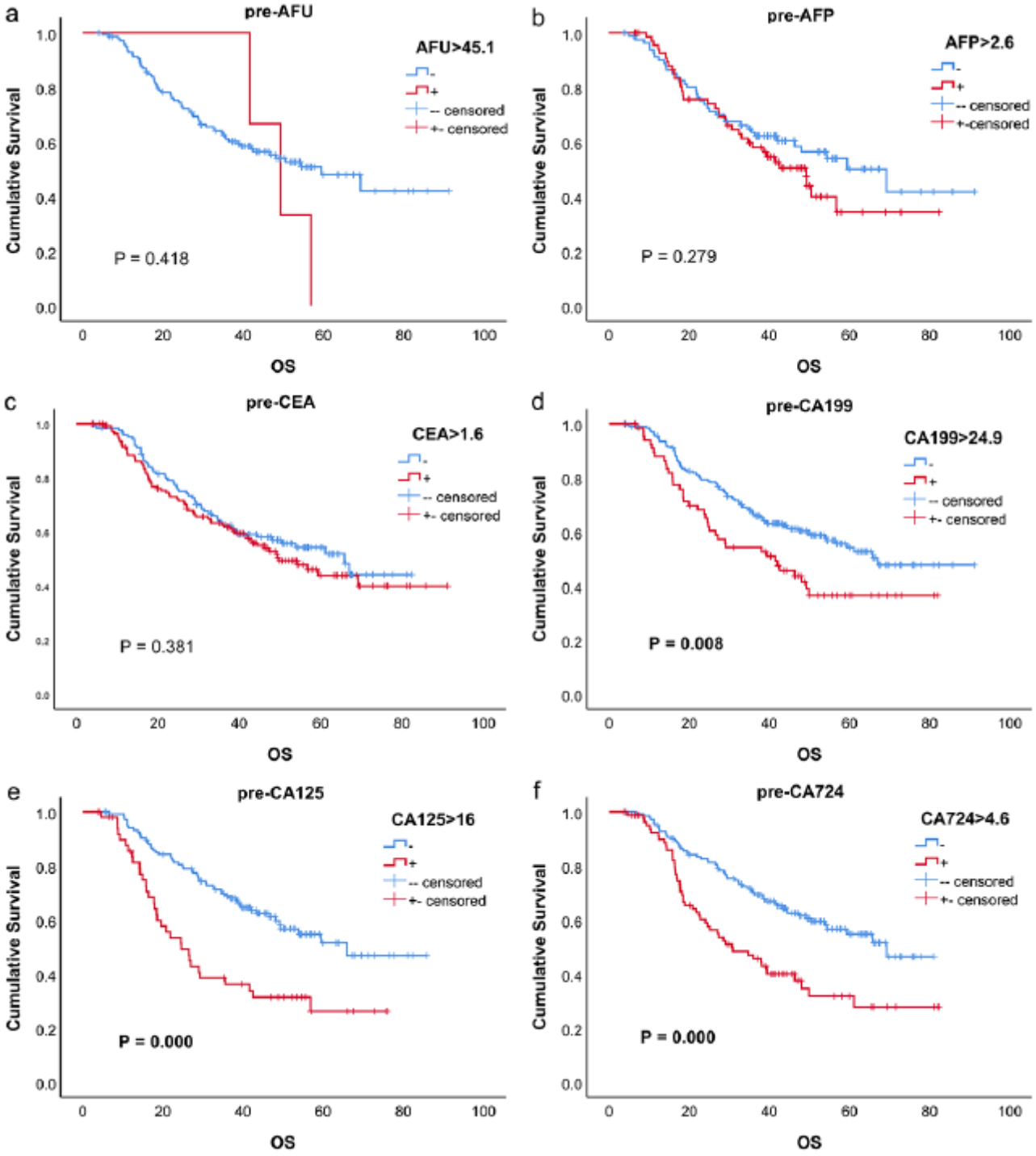

Figure 1

Kaplan–Meier curves of six tumor markers before neoadjuvant therapy.

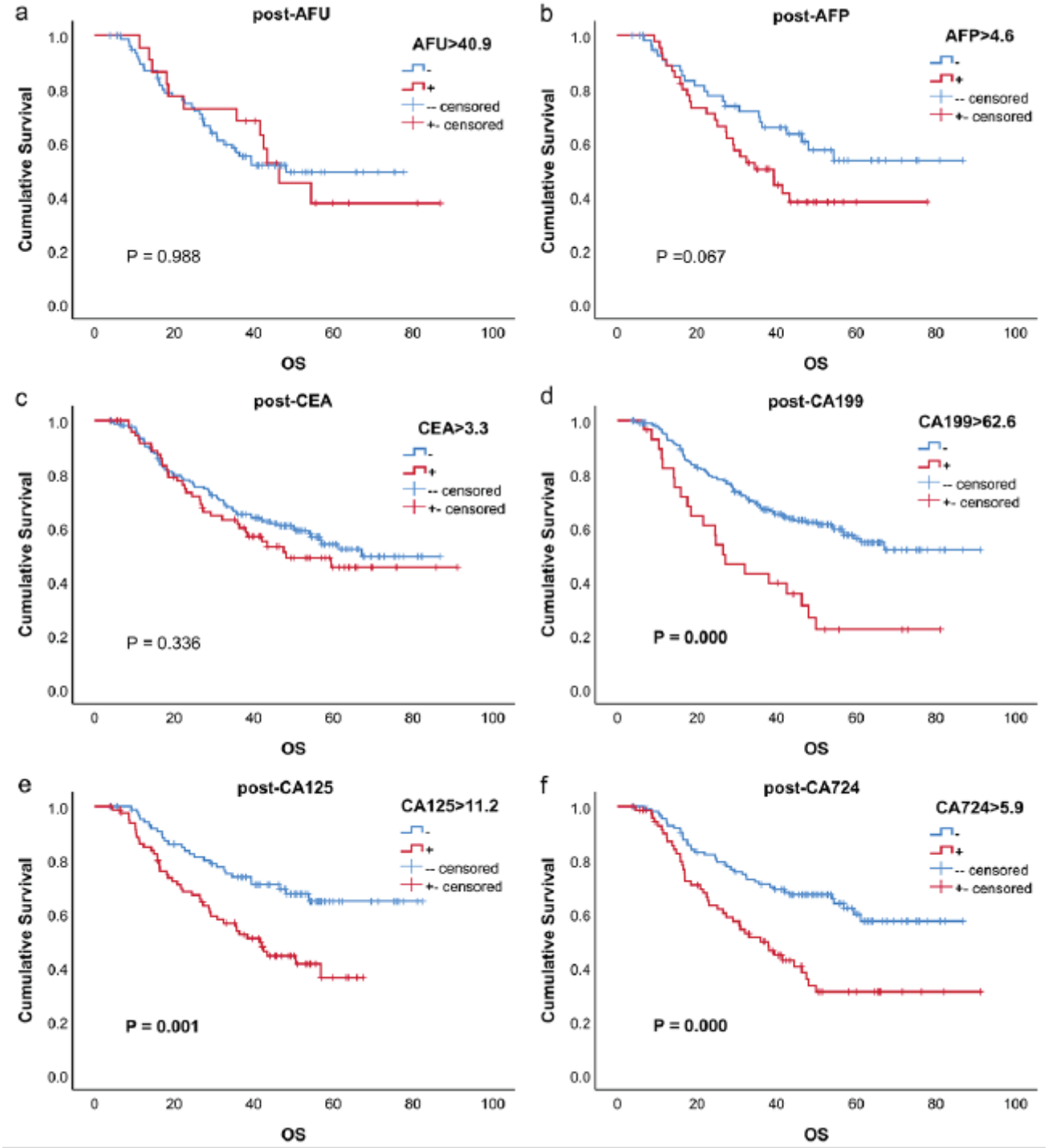

Figure 2

Kaplan–Meier curves of six tumor markers after neoadjuvant therapy.

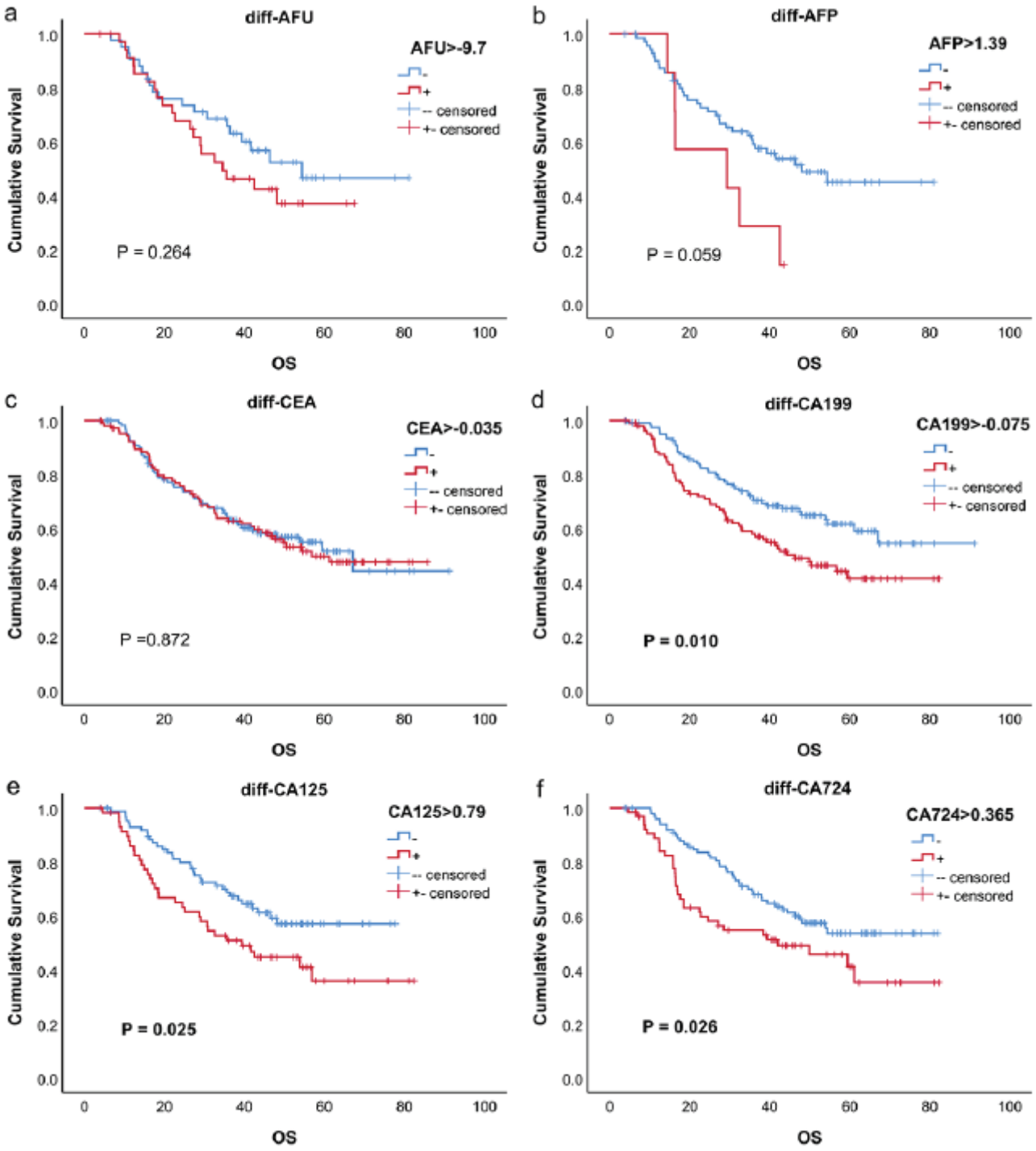

Figure 3

Kaplan–Meier curves of the change of six tumor markers due to neoadjuvant therapy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx